REMARKS

Claim 8 is pending in this application. Claim 8 has been rejected. No new matter has been added. Applicants are respectfully requesting reconsideration in view of the following remarks.

I. Withdrawn Rejections

Applicants acknowledge the withdrawal of the rejections under 35 U.S.C. 112, first and second paragraphs, and under 35 U.S.C. 102(b) in view of Schütt et al. (2002), Öllinger et al. (1995) or Weeks et al. (1996).

II. Rejection Under 35 U.S.C. §103(a)

Claim 8 has been rejected under 35 U.S.C. 103(a) as being unpatentable over Yoshida et al. ((1996) *Cancer Res.* 56:2945-2948) in view of Bard et al. ((1977) *Br. J. Cancer* 35:115-119). Yoshida et al. are suggested to teach a method of identifying an agent that increases oncogenic protein degradation by contacting an APL (acute promyelocytic leukemia) cell that expresses PML/RARα with the anti-cancer agent ATRA (all-*trans*-retinoic acid) and detecting whether ATRA increases PML/RARα protein degradation. It is acknowledged that Yoshida et al. do not teach a method for identifying and agent which destabilizes lysosomes comprising contacting a cell that expresses PML/RARα with an agent and detecting whether the agent destabilizes lysosomes of the cell as determined by vital staining of lysosomes or release of lysosomal proteins into the cytosol. Bard et al. are suggested to compensate by teaching a method wherein cartilage

cells are contacted with known anticancer retinoid compounds and detecting whether the retinoids destabilize lysosomes as determined by the release of lysosomal proteins into the cytosol and the resulting degradation of the cartilage matrix as a measure of toxicity. The Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the method of Yoshida et al. for identifying an anti-cancer agent that increases oncogenic protein degradation with the method of Bard et al. for identifying an anti-cancer agent which destabilizes lysosomes because it is *prima facie* obvious to combine two methods, each taught separately as useful for screening the same anti-cancer agent (retinoic acid) in order to form a single combined assay for detecting an anti-cancer agent which both destabilizes lysosomes and increases PML/RARα degradation.

Applicants respectfully traverse this rejection. While it is the Office's position that it would be obvious to combine the assays of Yoshida et al. and Bard et al., this reasoning completely disregards the explicit teaching away by Yoshida et al. of doing what the Office suggests. MPEP § 2143.03(VI) states that "[a] prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention." Accordingly, where cited art teaches away from a claimed feature, the cited art is not available for the purposes of an obviousness rejection.

In the instant case, the claims are directed to the identification of an agent that both destabilizes lysosomes and increases PML/RARα protein degradation. In contrast, Yoshida et

al. teach that ATRA accelerates the degradation of PML/RARα in the *nonlysosomal ubiquitin-proteasome pathway*. See the paragraph spanning pages 2946 and 2947. As such, there would be simply no motivation to determine whether lysosomes are destabilized as described by Bard et al., because Yoshida et al. provide a clear demonstration that ATRA-mediated PML/RARα degradation is by another mechanism. Therefore, Yoshida et al. teach away from the present invention because this reference suggests that developments flowing from its disclosures are unlikely to produce the objective of Applicants' invention (see *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)).

In so far as the skilled artisan, looking to develop an assay for identifying agents that destabilize lysosomes and increase PML/RARα degradation, would have no rationale for modifying the teachings of Yoshida et al. to monitor both PML/RARα degradation and lysosomal destabilization, the present invention cannot be considered obvious under 35 U.S.C. 103(a). It is therefore respectfully requested that this rejection be reconsidered and withdrawn.

III. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly,

favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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